

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Withdrawn): A method of causing cardiomyocyte growth and/or differentiation, the method comprising exposing a cardiomyocyte to neuregulin (NRG) thereby activating the MAP kinase pathway in the cardiomyocyte and causing growth and/or differentiation of the cardiomyocyte.
2. (Canceled): A method of inducing remodelling of cardiac muscle cell sarcomeric and cytoskeleton structures, or cell-cell adhesions, the method comprising treating cardiac muscle cells with neuregulin thereby activating the MAP kinase pathway in the cells and causing remodelling of the cell structures or the cell-cell adhesions.
3. (Withdrawn): The method according to claim 1 wherein neuregulin is provided directly to the cardiac cell or provided indirectly by causing neuregulin to be produced in other cells by inducing expression of the gene (s) involved in neuregulin production.
4. (Withdrawn): The method according to claim 1 wherein neuregulin production is in the cardiac muscle cell to which the method is directed in an autocrine manner or produced by some other cell and released in a paracrine manner.
5. (Withdrawn): The method according to claim 1 wherein function of a normal or diseased heart is improved by the treatment with neuregulin.
6. (Withdrawn): A method of identifying polypeptides or compounds which stimulate cardiac muscle cell differentiation, the method comprising contacting the cardiac muscle with a test polypeptide or compound in the presence of an inducer of cardiac muscle cell proliferation in the form of neuregulin, and measuring the development of cardiac muscle cell differentiation.

7. (Withdrawn): The method according to claim 6 wherein the differentiation of cardiac muscle cells is measured in cells exposed to neuregulin or other test polypeptides, or to a mixture of neuregulin with a test polypeptide.

8. (Withdrawn): The method according to claim 6 wherein differentiation of cardiac muscle cell is measured by a test selected from the group consisting of calculation of increases or decreases in DNA synthesis, analysis of the timecourse of phosphorylation of MAP kinases in cardiac muscle cells, evaluation of the expression of cell cycle inhibitor, p21^{CIP1}, phenotypic organisation of contractile units, accumulation of contractile units, phenotypic alteration of cytoskeleton actin fibers, and phenotype of cell-cell adhesions.

9. (Withdrawn): The method according to claim 6 wherein cells are incubated with different concentrations of various peptides or compounds and the effect of the test peptide or compound in different concentrations on cardiac muscle cell differentiation is measured.

10. (Withdrawn): The method according to claim 6 wherein cells are incubated with IGF-1, with and without the test polypeptide or compound, and the ability of the test polypeptide or compound to inhibit IGF-1-mediated cardiac muscle cell DNA synthesis, assembly of sarcomeric structures and cell-cell adhesions are measured.

11. (Withdrawn): The method according to claim 6 wherein the cells are incubated with phenylephrine (PE) with and without the test polypeptide or compound, and the ability of the test polypeptide or compound to augment PE-mediated cardiac muscle cell differentiation is determined.

12. (Withdrawn): The method according to claim 6 wherein the test polypeptide stimulates cardiac muscle cell differentiation and stimulates the assembly of sarcomeres thus enhancing heart function by activating neuregulin-specific receptors ErbB2, ERbB3 and ErbB4.

13. (Withdrawn): A method of identifying polypeptides or compounds which inhibit neuregulin stimulation of ventricular muscle cell differentiation, the method comprising contacting

the ventricular muscle cell with the test polypeptide or compound in the presence neuregulin and measuring any inhibition of neuregulin stimulation of the ventricular muscle cell.

14. (Withdrawn): The method according to claim 13 wherein the compound inhibits neuregulin stimulation of ventricular muscle cell differentiation by blocking, suppressing, reversing, or antagonising the action of neuregulin.

15. (Withdrawn): The method according to claim 14 wherein the measurement is by detecting DNA synthesis of ventricular muscle cells.

16. (Canceled): A therapeutic method of treating or preventing disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures in a mammal, the method comprising administering to the mammal a therapeutically effective amount of a neuregulin or its derivatives.

17. (Canceled): The method according to claim 16 wherein the therapeutic method is directed to treating heart failure resulting from disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures in the mammal.

18. (Withdrawn): A method of preventing or lowering the incidence of heart disease in a mammal, the method comprising preventing or lowering the interference or effects of polypeptides or compounds on the action of neuregulin and its receptors, ErbBs, that produces heart failure.

19. (Withdrawn): Use of therapeutic agent which mimics the effects of neuregulin to treat or prevent PE, or IGF-I-mediated cardiac muscle cell dysfunction.

20. (Withdrawn): A method of determining predisposition to heart disease or heart failure in a subject, the method comprising testing cardiac or related muscle cells of the subject for the ability to express and/or produce normal or adequate levels of neuregulin or its cognate ErbB receptors.

21. (Withdrawn): The method according to claim 20 wherein the inability to express and/or produce normal or adequate levels of neuregulin being indicative of predisposition to heart disease or heart failure.

22. (Withdrawn): Use of neuregulin, neuregulin polypeptide, neuregulin derivatives, or compounds which mimic the activities of neuregulins in the treatment or management of heart disease and heart failure in a mammal.

23. (Withdrawn): The use according to claim 22 wherein the concentration of neuregulin, neuregulin polypeptide, neuregulin derivatives, or compounds which mimic the activities of neuregulins is at least 10^{-8} M.

24. (Withdrawn): Use of neuregulin, neuregulin polypeptide, neuregulin derivatives, or compounds which mimic the activities of neuregulins in the manufacture of a medicament for the treatment or management of heart disease and heart failure.

25. (Canceled): The method according to claim 2 wherein neuregulin is provided directly to the cardiac cell or provided indirectly by causing neuregulin to be produced in other cells by inducing expression of the gene (s) involved in neuregulin production.

26. (Canceled): The method according to claim 2 wherein neuregulin production is in the cardiac muscle cell to which the method is directed in an autocrine manner or produced by some other cell and released in a paracrine manner.

27. (Canceled): The method according to claim 2 wherein neuregulin production is in the cardiac muscle cell to which the method is directed in an autocrine manner or produced by some other cell and released in a paracrine manner.

28. (Withdrawn): The method according to claim 3 wherein function of a normal or diseased heart is improved by the treatment with neuregulin.

29. (Withdrawn): The method according to claim 4 wherein function of a normal or diseased heart is improved by the treatment with neuregulin.

30. (New) A method of inducing remodeling of cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions, which method comprises contacting cardiac muscle cells with a neuregulin protein, or a functional fragment thereof, or a nucleic acid encoding a neuregulin protein, or a functional fragment thereof, in an amount sufficient to activate the MAP kinase pathway in said cardiac muscle cells and induce remodeling of said cardiac muscle cell sarcomeric and cytoskeleton structures or cell-cell adhesions.

31. (New) The method of claim 30, wherein the neuregulin carries out its activity via binding with ErbB2-ErbB3 or ErbB2-ErbB4 receptors.

32. (New) The method of claim 30, wherein the neuregulin fragment comprises an EGF-like domain.

33. (New) The method of claim 31, wherein the neuregulin fragment is a neuregulin β 2 fragment containing an EGF-like domain.

34. (New) The method of claim 33, wherein the neuregulin β 2 fragment comprising an amino acid sequence set forth in SEQ ID NO:2.

35. (New) The method of claim 30, wherein a neuregulin protein, or a functional fragment thereof, is administered.

36. (New) The method of claim 30, wherein a nucleic acid encoding a neuregulin protein, or a functional fragment thereof, is administered.

37. (New) The method of claim 30, wherein the neuregulin protein, or a functional fragment thereof, or the nucleic acid encoding a neuregulin protein, or a functional fragment thereof, is used in an amount that is at least 10^{-8} M.

38. (New) The method of claim 30, wherein the cardiomyocyte or the cardiac muscle cells exist in a mammal.

39. (New) The method of claim 38, wherein the mammal is a human.

40. (New) The method of claim 39, wherein the human has or is suspected of having a heart failure.

41. (New) The method of claim 40, wherein the heart failure is a disease state selected from the group consisting of congestive heart failure, myocardial infarction, tachyarrhythmia, familial hypertrophic cardiomyopathy, ischaemic heart disease, idiopathic dilated cardiomyopathy and myocarditis.

42. (New) The method of claim 40, wherein the heart failure is in the form of ischaemic, congenital, rheumatic, or idiopathic.

43. (New) The method of claim 40, wherein the heart failure results from disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures in the mammal.

44. (New) The method of claim 38, wherein the neuregulin protein, or a functional fragment thereof, or the nucleic acid encoding a neuregulin protein, or a functional fragment thereof, is administered with a pharmaceutically acceptable carrier or excipient.

45. (New) The method of claim 30, wherein the contact of the cardiac muscle cells with the neuregulin protein, or a functional fragment thereof, or the nucleic acid encoding a neuregulin protein, or a functional fragment thereof, decreases DNA synthesis in the cardiac muscle cells.

46. (New) The method of claim 30, wherein the contact of the cardiac muscle cells with the neuregulin protein, or a functional fragment thereof, or the nucleic acid encoding a neuregulin protein, or a functional fragment thereof, results in sustained activation of the MAP kinase pathway in the cardiac muscle cells.

47. (New) The method of claim 38, wherein the neuregulin protein, or a functional fragment thereof, or the nucleic acid encoding a neuregulin protein, or a functional fragment thereof, is administered orally, using a sustained-release system or via injection or infusion.

48. (New) The method of claim 47, wherein the injection or infusion is selected from the group consisting of intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial and intralesional injection or infusion.

49. (New) The method of claim 30, which further comprises contacting the cardiac muscle cells with an effective amount of an agent which causes cardiac hypertrophy or congestive heart failure.

50. (New) The method of claim 49, wherein the agent which causes cardiac hypertrophy or congestive heart failure is fludrocortisone acetate or herceptin.

51. (New) The method of claim 30, which further comprises contacting the cardiac muscle cells with an effective amount of an agent that acts to suppress a hypertrophy induction pathway different from the pathway suppressed by the neuregulin.

52. (New) The method of claim 51, wherein the agent that acts to suppress a hypertrophy induction pathway different from the pathway suppressed by the neuregulin is selected from the group consisting of a cardiostrophic inhibitor, an angiotensin-converting enzyme (ACE) inhibitor, a human growth hormone, an IGF-I, an anti-hypertrophic, myocardiostrophic factor, an anti-arrhythmic factor and an inotropic factor.

53. (New) The method of claim 30, which further comprises contacting the cardiac muscle cells with an effective amount of an angiotensin-converting enzyme (ACE) inhibitor.

54. (New) The method of claim 53, wherein the ACE inhibitor is selected from the group consisting of quinapril, ramipril, captopril, benazepril, fosinopril, lisinopril, enalapril and lisinopril.

55. (New) The method of claim 30, which further comprises contacting the cardiac muscle cells with an effective amount of an agent for treating hypertension.

56. (New) The method of claim 55, wherein the agent for treating hypertension is selected from the group consisting of an antibody to the endothelin receptor, a β -adrenoreceptor antagonist, an α_1 -noreceptor antagonist, an anti-oxidant, a β -blocker and a growth hormone.

57. (New) A method for treating or delaying disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures in a mammal, which method comprises administering to a mammal, to which such treatment or delay is needed or desirable, a neuregulin protein, or a functional fragment thereof, or a nucleic acid encoding a neuregulin protein, or a functional fragment thereof, in an amount sufficient to activate the MAP kinase pathway in said mammal, whereby said disassociation of cardiac muscle cell-cell adhesion and/or the disarray of sarcomeric structures is treated or delayed in said mammal.